Objectives: The aim of this study was to determine LV systolic and diastolic function and their association with circulating inflammatory markers in CIA.

Methods: Male Sprague Dawley rats were randomly divided into two groups: a control group (n=12) and a collagen-induced arthritis group (CIA, n=21). Rats in the CIA group were immunised with 0.2 ml type-II bovine collagen emulsified in incomplete Freund's adjuvant at the base of the tail followed by a 0.1 ml booster injection 7 days later. Eight weeks post-immunisation, markers of LV systolic function and geometry including ejection fraction (EF), fractional shortening (FS), stroke volume (SV) and LV end systolic diameter (ESD) were assessed echocardiographically using two-dimensional directed M-mode imaging. Markers of LV diastolic function including the early-to-late diastolic filling velocity ratio (E/A), the lateral (Lat e') and septal (Sep e') wall myocardial tissue lengthening at the mitral annulus and the ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e') were assessed using pulsed Doppler and tissue Doppler echocardiography. Serum concentrations of interleukin 6 (IL-6), interleukin 1 β (IL-1 β), tumour necrosis factor alpha (TNF- α) and C-reactive protein (CRP) were determined by an enzyme-linked immunosorbent assay.

Results: No significant differences in markers of systolic function or geometry (EF, FS, SV and ESD) were observed between the groups ($p>0.05$). Compared to the control group, E/A (control=2.17 $\pm$ 0.39; CIA=1.46 $\pm$ 0.46; $p=0.0001$) and Sep e' (control=3.75 $\pm$ 0.69; CIA=3.23 $\pm$ 0.47; $p=0.04$) were lower in the CIA group. By contrast, E/e' (control=29.94 $\pm$ 6.99; CIA=24.17 $\pm$ 8.49; $p=0.13$) and Lat e' (control=3.99 $\pm$ 0.43; CIA=3.79 $\pm$ 0.78; $p=0.31$) did not differ amongst the two groups. IL-6 (115 $\pm$ 70.09 versus 365.3 $\pm$ 88.96 pg/mL; $p<0.0001$), IL-1 β (14.1 $\pm$ 55.7 versus 238.6 $\pm$ 49.01 pg/mL; $p<0.0001$), TNF- α (293.5 $\pm$ 87.16 versus 626.0 $\pm$ 119.7 pg/mL; $p<0.0001$) and CRP concentrations (0.23 $\pm$ 0.34 versus 0.97 $\pm$ 0.35 ng/mL; $p<0.0001$) were higher in the CIA compared to control group. A lower E/A was associated with TNF- α ($r=-0.63$; $p=0.0003$), IL-6 ($r=-0.56$; $p=0.0001$), IL-1 β ($r=-0.48$; $p=0.001$) and CRP concentrations ($r=-0.60$; $p=0.001$) in the total sample. Lower TNF- α ($r=-0.39$ $p=0.04$) and IL-1 β ($r=-0.47$, $p=0.01$) levels were associated with E/e' in the total sample.

Conclusions: Diastolic function is impaired in male Sprague Dawley rats with CIA. Our results indicate that exposure to high grade inflammation can reduce LV relaxation without impairing systolic function in CIA. Markers of inflammation were also associated with increased filling pressures in this animal model. Systemic inflammation may directly impact myocardial diastolic function in CIA.

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THU0083 CD30 APTAMER-SLAT-SHRNA CHIMAERAS INHIBIT TH17 DIFFERENTIATION BY ROR γ T IN RHEUMATOID ARTHRITIS

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Background: T helper 17 (Th17) cells play a central role in rheumatoid arthritis (RA) via the production of pro-inflammatory cytokines interleukin (IL)-17. SWAP-70-like adapter of T cells (SLAT) has recently emerged as an important regulator of Th17 differentiation. Aptamer-facilitated cell specific delivery of shRNA represents an attractive novel approach for efficient RNAi delivery. However, the role of CD30 aptamer-SLAT-shRNA chimaeras in regulating Th17 differentiation in patients with RA is unclear.

Objectives: SLAT play a crucial role in regulating Th17 cell differentiation and function. This study was undertaken to investigate the role and mechanism of SLAT in Th17 cells differentiation in patients with RA.

Methods: Peripheral blood CD4⁺ T cells and synovial fluid CD4⁺ T cells derived from RA patients and healthy controls were used to test the effect of SLAT *in vitro*. CD30 aptamer-SLAT-shRNA chimaeras were generated *in vitro* and transfected into CD4⁺ T cells. The effect of CD30 aptamer-SLAT-shRNA chimaeras on Th17 production and differentiation was detected.

Results: SLAT was expressed mostly in cytoplasm and cell membrane of CD4⁺ T cells. The protein levels of SLAT in peripheral blood and synovial fluid CD4⁺ T cells of RA patients were higher than that of healthy controls. The effect of CD30 aptamer-SLAT-shRNA chimaeras on Th17 differentiation was due to its ability to sequester SLAT and prevent it from targeting the transcription factor ROR γ T.

Abstract THU0083 – Figure 1. A. SLAT was expressed mostly in cytoplasm and cell membrane of CD4⁺ T cells. D. CD30 aptamer-SLAT-shRNA chimaeras reduced the percentage of CD4⁺ROR γ T⁺ T cells and CD4⁺IL-17⁺ T cells.

Conclusions: This study reveals new evidence of the role of SLAT in Th17 differentiation in CD4⁺ T cells of RA patients.

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THU0084 HISTONE DEACETYLASE 1 (HDAC1): A NOVEL THERAPEUTIC TARGET IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Despite enormous efforts to develop new therapeutic strategies for treatment of rheumatoid arthritis (RA), the large number of non responding

patients to currently available drugs underlies the unmet need to identify new therapeutic targets.

Objectives: Certain CD4⁺T cell subsets, especially Th17 cells, have been shown to be major drivers of inflammation in patients with RA. The expression of their key transcription factors is controlled by histone modifications which includes acetylation of *lysine residues* mediated by histone deacetylases (HDAC). Indeed, pan HDAC inhibitors have been shown to be a potential therapeutic strategy. However, major side effects limited the clinical use and underline the need of more specific HDAC inhibitors. We therefore addressed the individual role of HDAC1 on the development of collagen-induced arthritis model (CIA).

Methods: Mice with a T cell specific deletion of HDAC1 (HDAC1 cKO) were generated by using the CD4Cre/LoxP system. Collagen induced arthritis (CIA) was induced at week 8. Animals were scored for paw swelling and grip strength. After 10 weeks, mice were sacrificed and paraffin sections of the affected joints were analysed for histomorphologic signs of inflammation, cartilage and bone destruction. Anti-CII antibody levels were determined by ELISA. Serum samples were analysed for various cytokines by multiplex assays. CCR6 expression in CD4 T cells was analysed by flow cytometry.

Results: To address potential effects of HDAC1 in the pathogenesis of RA, CIA was induced in HDAC1cKO mice and WT mice. Surprisingly HDAC1cKO mice were completely protected from the development of arthritis. In line with the clinical data, histological analysis revealed no signs of inflammation, no bone erosion and no osteoclasts in the joints of HDAC1cKO mice. Anti-CII antibodies, including total IgG and IgG2c were detected in HDAC1cKO and WT mice. Surprisingly, IL-17 was significantly decreased in the serum of HDAC1 cKO mice as compared to WT mice, suggesting a role of HDAC1 in the development of Th17 cells. To see whether HDAC1 is involved in the regulation of the chemokine receptor 6 (CCR6), the main marker of Th17 cells, we compared the upregulation of CCR6 in CD4⁺ T cells from WT and HDAC1cKO mice. Indeed, CCR6 could not be upregulated in CD4⁺ T cells from HDAC1cKO mice upon IL-6 *in vitro*. These data support the role of HDAC1 in the regulation of CCR6, an important chemokine receptor, which is necessary for the migration of pathogenic Th17 cells and therefore for the development of arthritis.

Conclusions: Our data show the importance of HDAC1 as a key immune regulator in the pathogenesis of T cell driven collagen induced arthritis. Therefore, it might be considered as an interesting novel therapeutic target in RA.

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THU0085

CR6086, A NOVEL EP4 ANTAGONIST WITH IMMUNOMODULATORY PROPERTIES, DECREASES BONE LOSS IN THE RAT COLLAGEN-INDUCED ARTHRITIS (CIA) MODEL: A MICROTOMOGRAPHY (MICROCT) STUDY

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Background: CR6086 is a novel PGE2 EP4 receptor antagonist showing favourable immunomodulatory properties, striking DMARD effects in rodents, and an anti-inflammatory activity targeted to immune-mediated diseases and distinct from that of NSAIDs. Besides its role in controlling T cells, PGE2 is implicated in the aggressive bone erosion of rheumatoid arthritis (RA).

Objectives: To characterise CR6086 activity on the bone compartment mostly affected by erosion in the CIA model in rats.

Methods: 15 male Lewis rats were immunised by intradermal injection with collagen II in CFA. 5 naïve animals were the sham group. 3 days after boost, oedema was assessed and rats assigned to treatment with vehicle or CR6086 (3 or 10 mg/kg qd). Oedema was measured again on days 7 and 14, and hindlimb joints were blindly scored for clinical signs of arthritis (scale 0–4; from normal=0 to maximally inflamed limb with involvement of multiple joints=4). At sacrifice, hindlimb calcaneus underwent high-resolution X-ray microCT (total and cancellous bone), a sensitive method that allows the reduction of experimental animals in compliance with the 3R rule. Parameters were expressed as the mean of left and right paw. Joints were then scored for histological features. Statistics were performed by ANOVA, correlations by Spearman analysis.

Results: CR6086 significantly reduced bone loss in CIA rats (table 1), even at the low dose of 3 mg/kg. The effect on cancellous bone plateaued already at 3 mg/

kg, confirming the sensitivity of the metabolically more active districts of bone to the action of EP4 antagonists.

	Sham-vehicle	CIA-vehicle	CIA-CR6086 3mpk	CIA-CR6086 10mpk
Total bone, mean (SD)				
BMD (mg/cm³)	277.20 (1.25)	267.40 (0.95)	273.50 (2.09) p 0.0004#, 0.0167\$	273.90 (2.17) p 0.0002#, 0.0322\$
BV/TV (%)	82.53 (10.11)	60.64 (2.68)	76.02 (5.57) p 0.0005#, n.s.\$	76.77 (5.30) p 0.0003#, n.s.\$
BS/BV (mm⁻¹)	6.10 (0.78)	13.64 (0.83)	9.00 (1.48) p 0.0001#, 0.0044\$	8.61 (1.25) p 0.0001#, 0.0134\$
Cancellous bone, mean (SD)				
BMD (mg/cm³)	270.44 (2.17)	261.20 (1.20)	267.31 (1.87) p 0.0007#, n.s.\$	266.24 (2.61) p 0.0032#, 0.0225\$
BV/TV (%)	71.09 (4.99)	42.76 (3.74)	61.66 (6.81) p 0.0009#, n.s.\$	58.17 (7.57) p 0.0040#, 0.0165\$
BS/BV (mm⁻¹)	14.51 (2.67)	30.31 (1.84)	20.83 (3.30) p 0.0008#, 0.0196\$	21.84 (3.81) p 0.0019#, 0.0067\$
Trabecular thickness (µm)*	143.02 (31.94)	66.94 (4.39)	98.49 (14.38) p 0.0041#, 0.0111\$	94.25 (16.38) p 0.0105#, 0.0055\$
Trabecular separation (µm)**	56.46 (3.51)	90.85 (9.00)	60.51 (8.85) p 0.0004#, n.s.\$	66.85 (9.28) p 0.0023#, n.s.\$
Trabecular number (mm⁻¹)	3.64 (0.39)	3.31 (0.10)	4.01 (0.26) p 0.0001#, n.s.\$	3.93 (0.13) p 0.0003#, n.s.\$

*) 2x(BV/BS); **) 2x(TV-BV)/BS; \$ vs. sham; # vs. CIA; BMD, Bone Mineral Density; TV, Total Volume; BV, Bone Volume; BS, Bone Surface; mpk, mg/kg
There was a strict correlation between clinical score and bone parameters (BMD; figure 1 inset), confirming that bone erosion in CIA is closely associated with arthritis severity.

Conclusions: CR6086 is an EP4 antagonist in clinical development for RA (NCT03163966). Besides its immunomodulatory activity, CR6086 effectively decreases the aggressive bone erosion that characterises both the CIA model and the early phases of human RA.

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